# Treatment of multidrug-resistant Gram-negative bloodstream infections in critically ill patients: an update

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**Purpose of review**
This review describes the latest information in the management of bloodstream infections caused by multidrug-resistant Gram-negative bacilli (MDRGNB) in critically ill patients.

**Recent findings**
The prevalence of bloodstream infections due to MDRGNB is high, and they pose a significant risk in critically ill patients. Recently, novel antimicrobial agents, including new β-lactam/β-lactamase inhibitor combinations and cefiderocol, have been introduced for treating these infections. Concurrently, updated guidelines have been issued to aid in treatment decisions. Prompt diagnosis and identification of resistance patterns are crucial for initiating effective antibiotic therapy. Current studies, especially with observational design, and with limited sample sizes and patients with bacteremia, suggest that the use of these new antibiotics is associated with improved outcomes in critically ill patients with MDRGNB bloodstream infections.

**Summary**
For critically ill patients with bloodstream infections caused by MDRGNB, the use of newly developed antibiotics is recommended based on limited observational evidence. Further randomized clinical trials are necessary to determine the most effective antimicrobial therapies among the available options.

**Keywords**
bloodstream infection, critical illness, multidrug resistance, practice guidelines

## INTRODUCTION

Bloodstream infections (BSI) are among the most prevalent and potentially life-threatening conditions in healthcare settings. Their incidence in intensive care units (ICUs) varies depending on the severity of the underlying illness, exposure to invasive devices, and the presence of risk factors such as immunosuppression or recent surgical procedures [1,2]. Most ICU-acquired BSIs are related to intravascular catheter infection, intra-abdominal infection, and ventilator-associated pneumonia, though no definite source is identified for a substantial proportion of cases [2]. BSI is associated with notably high mortality rates, ranging from 30% to 60%. BSI also prolongs ICU stay and escalates healthcare costs [3,4▪,5]. In addition, in recent decades there has been a worrying increase in BSI caused by resistant pathogens in ICUs. Critically ill ICU-admitted patients are particularly prone to developing infections due to multidrug-resistant Gram-negative bacilli (MDRGNB). This widespread emergence of MDRGNB has often rendered standard empiric treatment approaches ineffective, thereby exacerbating morbidity and mortality rates [6]. The distribution of BSI caused by MDRGNB varies substantially depending on patient characteristics, sources of infection, and geographical area. In response to the increase in resistance, new antimicrobial drugs (including new β-lactam/β-lactamase inhibitor combinations and cefiderocol) have

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## KEY POINTS

- The incidence of multidrug-resistant Gram-negative bloodstream infections (MDRGNB) has increased significantly.
- The use of new antibiotics, including β-lactam/β-lactamase inhibitor and cefiderocol, is associated with improved outcomes in MDRGNB.
- Most evidence comes from observational studies; randomized studies that evaluate clinical outcomes are needed.

been introduced for therapeutic use. Moreover, several scientific societies have developed guidelines for the treatment of infections caused by MDR-GNB (Table 1) [7▪▪,8▪▪,9,10]. Consistent epidemiological surveillance, enforcement of preventive measures, early microbiological diagnosis and source control, optimization of antibiotic therapy and antimicrobial de-escalation strategies are imperative in order to limit the spread of antibiotic resistance and to improve clinical outcomes in critically ill ICU patients with infections due to MDRGNB [11–13].

This review provides updated information on the treatment of BSI caused by MDRGNB in critically ill patients.

## Treatment of extended-spectrum β-lactamase-producing Enterobacterales

Extended-spectrum β-lactamases (ESBLs) are enzymes that break down expanded-spectrum cephalosporins (third- and fourth generation cephalosporins) and monobactams, but not cephamycins or carbapenems. Pathogens carrying ESBL genes often possess additional genes or mutations that confer resistance to a broad range of nonβ-lactam antibiotics [14,15]. Nonsusceptibility to ceftriaxone is often used as an indicator of ESBL production, although its specificity is limited [8▪▪]. In the past, TEM- and SHV-type ESBLs were the most frequently found, but today CTX-M-type enzymes predominate [14,15].

Between 2012 and 2017, the SENTRY Antimicrobial Surveillance Program assessed the frequency of occurrence and antimicrobial susceptibility profiles of 6741 bacterial and 222 fungal pathogens causing BSI across 16 medical centers worldwide [16]. *E. coli* and *Klebsiella* spp. showed similar rates of resistance to expanded-spectrum cephalosporins with minimal changes over time. BSIs caused by ESBL-producing *Klebsiella* spp. were more common in ICU patients (29.4%) than in non-ICU patients (18.6%). Conversely, ESBL-producing *E. coli* was more prevalent in non-ICU patients (61.3% vs. 40.4%) [17]. Other studies have reported ESBL frequencies ranging from 36.3% to 92% in critically ill patients with BSI caused by *E. coli* and *Klebsiella* spp. [18,19].

Current guidelines recommend the use of carbapenems (meropenem or imipenem) for BSI or severe infections caused by ESBL-producing Enterobacterales in critically ill patients [7▪▪,8▪▪]. Although observational studies show no differences in outcomes between piperacillin/tazobactam and carbapenems [20], this recommendation is mainly based on the results of the MERINO trial, which compared piperacillin-tazobactam with meropenem in patients with BSI caused by third generation cephalosporin-resistant *E. coli* and *K. pneumoniae* [21]. Piperacillin-tazobactam did not demonstrate noninferiority, presenting higher 30-day mortality rates than meropenem. Moreover, for ESBL-BSIs without certain features (septic shock, critical illness, central nervous system infection or hypoalbuminemia), ertapenem may be an alternative to imipenem or meropenem [22,23]. A higher dose of ertapenem has been recommended for patients with high-inoculum infections [20]. Once clinical response is achieved and concerns about intestinal absorption are addressed, de-escalation to trimethoprim-sulfamethoxazole (TMP-SMX) or fluoroquinolones may be considered if susceptibility is confirmed [7▪▪,8▪▪,24].

International consensus recommends the use of extended or continuous infusion of β-lactam antibiotics rather than short infusion in order to reduce mortality or increase clinical cure rates among severely ill adult patients, particularly those with Gram-negative infections [25▪▪]. However, in a recent double-blind randomized control trial (RCT) conducted in 31 ICUs in four countries in critically ill patients with sepsis, the continuous administration of meropenem did not improve the composite outcome of mortality and emergence of multidrug resistant bacteria at day 28 compared with intermittent administration [26].

## Treatment of AmpC β-lactamase-producing Enterobacterales

AmpC β-lactamase resistance can be categorized into three types: (a) inducible resistance through chromosomally encoded AmpC genes, (b) noninducible chromosomal resistance due to mutations in promoters and/or attenuators, and (c) plasmid-mediated resistance. AmpC β-lactamases are enzymes that confer resistance to penicillins, second and third generation cephalosporins, and cephamycins. Cefepime and carbapenems typically maintain high efficacy against AmpC-producing isolates when other relevant β-lactamases are absent (e.g., ESBLs or carbapenemases).



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**Table 1.** Guideline recommendations for the antibiotic treatment of bloodstream infections due to multidrug-resistant Gram-negative bacilli

| | IDSA [8▪▪] | ESCMID [7▪▪] | SEIMC [10] | CMA [9] |
|---|---|---|---|---|
| ESBL-producing Enterobacterales | Carbapenem[a] | Carbapenem[a] | | |
| AmpC β-lactamase-producing Enterobacterales | High risk of clinically significant AmpC production: Cefepime | | | |
| Carbapenemase-producing Enterobacterales[b] | Ceftazidime-avibactam (± aztreonam), meropenem-vaborbactam, and imipenem-cilastatin-relebactam | Ceftazidime-avibactam (± aztreonam), meropenem-vaborbactam. Cefiderocol | Ceftazidime–avibactam (± aztreonam), meropenem–vaborbactam, imipenem–relebactam, cefiderocol | Ceftazidime-avibactam (± aztreonam) |
| Difficult to treat *P. aeruginosa* | Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam. Cefiderocol is an alternative[c] | Ceftolozane-tazobactam | Ceftolozane–tazobactam | |
| Carbapenem-resistant *A. baumannii* | High-dose ampicillin-sulbactam in combination with at least one other agent | Combination therapy including two in vitro active antibiotics. Susceptible to sulbactam: ampicillin/sulbactam. Resistant to sulbactam: polymyxin, tigecycline | High dose sulbactam in combination with additional antimicrobials | Sulbactam combination therapy. Tigecycline- or polymyxin-based combination therapy (pneumonia caused by CRAB). Choice of therapy regimen should be made according to patient's condition |
| *Stenotrophomonas maltophilia* | Combination therapy: TMP-SMX, minocycline/tigecycline, cefiderocol or levofloxacin; or ceftazidime-avibactam and aztreonam[d] | Combination therapy: TMP-SMX and levofloxacin | | |

CMA, Chinese Medical Association; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Disease Society of America; SEIMC, Sociedad Española de Enfermedades Infecciosas y Microbiologia Clinica.
[a]Meropenem or imipenem are the preferred therapies for bacteremia in critically ill patients.
[b]Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are recommended for KPC producing Enterobacteriaceae; Ceftazidime-avibactam is preferred for OXA-48 producing Enterobacteriaceae; Ceftazidime-avibactam plus aztreonam is recommended for carbapenem resistant Enterobacteriaceae carrying metallo-b-lactamases.
[c]For patients infected with DTR-P. aeruginosa isolates that are metallo-β-lactamase producing, the preferred treatment is cefiderocol.
[d]Ceftazidime-avibactam and aztreonam especially when there is clinical instability or when other medications are not well tolerated or are ineffective.

Exposure to cephalosporins can stimulate significant AmpC production and β-lactam resistance, even in initially susceptible isolates [27,28].

In the SENTRY Antimicrobial Surveillance Program, *Enterobacter spp*. was classed eighth among the top 10 BSI pathogens isolated from 2012 to 2017, a ranking that showed little change over time [16]. Resistance to cefepime among *Enterobacter spp*. isolates remained low and was also stable over this period. Similarly, Hu *et al.* [17] reported the prevalence of various pathogens isolated from BSI in China, with *Enterobacter* spp., *Serratia* spp., and *Citrobacter* spp. being the most frequent among Enterobacterales. A recent multicenter retrospective observational study analyzed AmpC pathogens isolated from blood cultures in 27 European hospitals (2020–2022) [29]. The most common species were *Enterobacter cloacae* complex (44.8%), *Serratia marcescens* (22.7%), and *K. aerogenes* (13.3%). Overall, these AmpC pathogens were found mainly in patients admitted to medical wards (37.2%) and ICUs (30.9%).



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The Infectious Disease Society of America (IDSA) guidelines recommend antibiotic treatment based on the risk of clinically significant AmpC production from an inducible AmpC gene [8▪▪]. *Enterobacter cloacae* complex, *Klebsiella aerogenes*, and *Citrobacter freundii* are the most common Enterobacterales with a moderate to high risk for clinically significant AmpC production. Cefepime is the recommended antibiotic for treating infections caused by these organisms. Unfortunately, there are no clinical trials comparing outcomes of patients treated with cefepime versus carbapenem therapy for AmpC infections. A meta-analysis of observational studies comparing clinical outcomes of patients receiving cefepime versus carbapenems for BSI caused by *Enterobacter spp*., *Citrobacter* spp., and *Serratia* spp. did not find significant differences in outcomes between these treatments [30]. However, there was considerable heterogeneity between the studies, with ill patients more likely to receive carbapenem therapy, and the risk of AmpC production varied according to the species included. Additionally, the studies did not provide complete information on the number and outcomes of critically ill patients or of those who present septic shock. Therefore, in critically ill patients or those with septic shock, carbapenems may initially be used. Moreover, ceftriaxone, cefotaxime, ceftazidime, and piperacillin/tazobactam are not recommended for invasive infections caused by organisms at moderate to high risk of clinically significant AmpC production [8▪▪,31].

Overexpression of AmpC occurs in fewer than 5% of other pathogens like *S. marcescens*, *M. morganii*, and *Providencia* spp. [8▪▪]. Thus, when these pathogens are identified in clinical samples, the IDSA guidelines advise choosing antibiotic treatment based on the susceptibility results. However, recent studies have shown an increased risk of treatment failure when antibiotic therapy is limited to third-generation cephalosporins [32,33]. In addition, guidelines recommend that in cases of infections with a high bacterial inoculum and limited source control, such as endocarditis or central nervous system infections, using cefepime instead of ceftriaxone may be considered [8▪▪].

TMP-SMX and fluoroquinolones are also options for patients with AmpC infections provided that susceptibility is demonstrated, patients are stable, source control measures are taken, and concerns about absorption are minimal [8▪▪,24].

## Treatment of carbapenemase-resistant Enterobacterales

Carbapenemase-resistant Enterobacterales (CRE) refers to Enterobacterales that are resistant to at least one carbapenem antibiotic, as determined by their antibiotic susceptibility profile. Guidelines now recommend testing for carbapenemases as well as antimicrobial synergy testing to treat CRE infections [7▪▪,8▪▪,32]. Carbapenem resistance can arise through various mechanisms, including chromosomal mutations in porin genes (noncarbapenemase-producing CRE) and/or the production of carbapenem hydrolysing enzymes (carbapenemase-producing CRE) [34,35,36].

The EUROBACT-2 study, conducted between June 2019 and February 2021, analyzed adult patients (≥18 years old) with hospital-acquired BSI across 333 ICUs in 52 countries [4▪]. The study found carbapenem resistance in 37.8% of *Klebsiella* spp., 22% of *Enterobacter* spp., and 7.4% of *E. coli* isolates. Compared to a previous study (EUROBACT, 2012) [3], carbapenem resistance has increased notably, especially in *Enterobacter* spp. Studies have found that hospital-acquired and ICU-associated BSIs show higher carbapenem resistance rates than community-acquired and non-ICU BSIs [3,4▪,17]. Another study analyzing eight-year trends in BSI in Greek hospitals (2010 to 2017) found increasing rates of carbapenem resistance in *E. coli*, *K. pneumoniae*, and *Enterobacter* spp. isolates from both hospital wards and ICUs [18].

The evidence available on antibiotic treatment for CRE primarily originates from observational studies involving patients who present diverse types of infection and varying degrees of clinical severity. These studies predominantly focused on infections attributed to KPC-producing *K. pneumoniae*, with only limited attention to OXA-48 producers, MBL noncarbapenemase producers, and CRE strains other than *K. pneumoniae*. No clinical trials comparing antibiotics for the treatment of CRE are currently available.

Ceftazidime-avibactam is recommended for infections caused by CRE-producing serine carbapenemases, such as KPC and OXA-48, and may be more effective than other treatments [7▪▪,8▪▪,9,10]. A meta-analysis of ten studies involving 833 patients (325 on ceftazidime-avibactam versus 508 on polymyxins) found that ceftazidime-avibactam reduced mortality and treatment failure risk in CRE-infected patients, with minimal adverse events, even in those with CRE bloodstream infections [37]. Studies have also shown ceftazidime-avibactam to be cost-effective for treating CRE BSI and pneumonia [38]. Meropenem-vaborbactam and imipenem-cilastatin-relebactam are also options for KPC-producing infections, while cefiderocol serves as an alternative [8▪▪]. Meropenem-vaborbactam and imipenem-cilastatin-relebactam are effective against most Enterobacterales producing KPC enzymes, but not against



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those producing OXA-48-like carbapenemases. In the TANGO-II trial, meropenem-vaborbactam has shown improved cure rates and nonsignificantly lower 28-day mortality in patients with CRE infections [39]. Cefiderocol has been reported to present similar efficacy and safety profiles to comparator antibiotics in critically ill patients in phase 3 clinical studies; however, conflicting results were seen in one study (CREDIBLE-CR), possibly due to baseline imbalances among patients with *A. baumannii* infections [40].

Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, are the preferred treatment for infections caused by MBL-producing pathogens. Although aztreonam is active against MBL, it can be affected by other enzymes (ESBLs, AmpC β-lactamases, KPCs, or OXA-48-like carbapenemases) often present in MBL-producing isolates. Avibactam generally remains effective in inhibiting the activity of these latter β-lactamase enzymes [7▪▪,8▪▪,9,10]. In a prospective observational study of patients with BSI due to MBL-producing Enterobacterales, 30-day mortality, clinical failure and length of hospital stay were lower for those treated with the combination of ceftazidime-avibactam and aztreonam [41]. Similarly, a subgroup analysis within the APEKS-NP and CREDIBLE-CR studies confirmed that cefiderocol offers effective treatment for infections caused by carbapenem-resistant Gram-negative bacteria carrying MBL enzymes. Results showed a clinical cure rate of 70.8% and a microbiological eradication rate of 58.3%. Additionally, mortality rates were not higher in these patients [42]. Moreover, aztreonam-avibactam had demonstrated potent activity against CRE isolates [43,44], but clinical data are limited. Recently, both the European Medicines Agency and the Food and Drug Administration have recommended granting marketing authorization for aztreonam-avibactam. This medication is intended for treating infections caused by aerobic Gram-negative bacteria in patients with limited treatment options, such as MBL-producing bacteria.

## Treatment of multidrug-resistant/difficult-to-treat resistance (DTR) *Pseudomonas aeruginosa*

The definition of MDR *P. aeruginosa* has evolved in recent years [45,46]. The concept of DTR *P. aeruginosa* was introduced in 2018, encompassing resistance to multiple antibiotics including piperacillin-tazobactam, cephalosporins, aztreonam, carbapenems, and fluoroquinolones [47]. *P. aeruginosa* resistance often occurs via more than one mechanism, including restricted outer membrane permeability, presence of antibiotic efflux systems, and the production of antibiotic-inactivating enzymes [45].

In the SENTRY Antimicrobial Surveillance Program, the prevalence of MDR *P. aeruginosa* was higher in Europe (18.8%) than in North America (13.1%) [16,17]. Overall, the prevalence of MDR *P. aeruginosa* was high (15.4%) but showed a decline from 2012 to 2017. Similar trends were observed in Greece regarding ICU BSIs, whereas in non-ICU wards the prevalence of MDR *P. aeruginosa* increased [18]. Additionally, the EUROBACT-2 study, which focused on adult patients with hospital-acquired BSI between 2019 and 2021, reported an increase in the prevalence of pan-drug resistant (resistance to all tested antibiotics) *P. aeruginosa* compared to the EUROBACT study conducted in 2012 [3,4▪].

Between 20% to 60% of carbapenem-resistant *P. aeruginosa* are susceptible to other noncarbapenem β-lactam agents. This resistance profile is often the result of a significant decrease in the production of OprD. Sometimes this resistance profile is accompanied by overexpression of efflux pumps [48]. There are no comparative effectiveness studies to guide treatment decisions for infections caused by carbapenem-resistant *P. aeruginosa* that are susceptible to other noncarbapenem β-lactam agents. Guidelines suggest using noncarbapenem β-lactam agents as high-dose extended-infusion therapy in these cases [8▪▪,10]. In addition, for critically ill patients or those with inadequate source control, guidelines recommend the use of novel β-lactams (ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam) as a reasonable option [8▪▪].

Moreover, there are no comparative data from RCTs on the effect of new antibiotics on DTR *P. aeruginosa*, and so clinical evidence on its management is extremely limited. For severe infections attributed to DTR *P. aeruginosa*, the recommended treatment options include ceftolozane-tazobactam [7▪▪,8▪▪,10], ceftazidime-avibactam and imipenem-cilastatin-relebactam [8▪▪,10]. Alternatively, cefiderocol can be considered as a treatment option [8▪▪,10]. Additionally, the Spanish Society of Infectious Diseases and Clinical Microbiology guidelines recommend considering combination therapy for severe DTR *P. aeruginosa* infections or those with a high bacterial load. The preferred approach involves combining a β-lactam agent like ceftolozane–tazobactam or ceftazidime–avibactam with an aminoglycoside or colistin [10].

For infections caused by DTR *P. aeruginosa* producing MBL, cefiderocol is the preferred therapy [8▪▪]. Combining ceftazidime-avibactam with aztreonam is unlikely to offer significant benefits for treating MBL-producing *P. aeruginosa* infections. Data extrapolated from aztreonam-avibactam studies suggest limited



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activity against MBL-producing *P. aeruginosa*, affecting fewer than 10% of cases [49].

When the new β-lactams are not available, polymyxins should be administered for invasive infections caused by DTR *P. aeruginosa* in combination with other antimicrobials to which the isolate was susceptible [7▪▪,8▪▪,9,10]. Aminoglycosides and IV fosfomycin at high doses (8 g IV q8 h) may be considered as part of a combination treatment for susceptible isolates.

### Treatment of carbapenem-resistant *Acinetobacter baumannii*

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has emerged as a leading cause of healthcare-associated infections. It prolongs hospital stays, raises ICU admission and readmission rates, and increases healthcare costs [50]. A systematic review comprising 62 779 cases found resistance rates to imipenem and meropenem to be 62% and 64% respectively. The highest resistance rate was observed in Asia (70% for meropenem), and the lowest in Europe (57% for meropenem) [51]. In the EUROBACT-2 study, carbapenem resistance was substantially higher among adult patients with hospital-acquired BSI (especially due to *Acinetobacter* spp.) than in the original EUROBACT study carried out 11 years earlier (rising from 68.7% to 84.6%) [3,4▪]. *A. baumannii* is intrinsically resistant to several antibiotics and easily acquires resistance to others; once carbapenem-resistant, it typically exhibits resistance to most other antibiotics effective against its wild-type form. Resistance mechanisms involve OXA carbapenemases, metallo-β-lactamases, and other serine carbapenemases (e.g., *A. baumannii*-derived cephalosporinases). Sulbactam resistance probably involves mutations affecting penicillin-binding proteins (PBPs) and β-lactamase production [8▪▪,52,53].

Two meta-analyses have assessed observational and clinical trial data on treatment options for CRAB infections [54,55]. Combination therapy is recommended for severe and high-risk CRAB infections, involving two antibiotics that are active in vitro. Sulbactam is the first-line treatment if *A. baumannii* is susceptible. High-dose ampicillin-sulbactam (9–12 g i.v. q8hs) or cefoperazone-sulbactam combined with another agent is suggested. Options for combination therapy include polymyxin B, minocycline, tigecycline, and aminoglycosides [7▪▪,8▪▪,9,10].

When ampicillin-sulbactam resistance is present, guidelines propose using a combination of polymyxin, high-dose minocycline, high-dose tigecycline, or aminoglycosides if they are active in vitro [7▪▪,9,10]. However, according to IDSA guidelines, ampicillin-sulbactam might still be effective due to sulbactam's ability to saturate altered targets [8▪▪]. There is no specific recommended combination supported by the evidence.

Cefiderocol is recommended for severe CRAB infections when treatment options are limited, typically in combination with other drugs [10]. Similarly, sulbactam-durlobactam is reserved for patients with hospital-acquired or ventilator-associated pneumonia, or BSIs caused by CRAB, when the isolate is resistant to other first-line agents. In a randomized trial involving 59 clinical sites across 16 countries, the sulbactam-durlobactam group experienced a mortality rate of 19% within 28 days, compared to 32% in the colistin group [56].

Moreover, meropenem, imipenem-cilastatin, fosfomycin, and rifampin are not recommended for combination therapy [57–59]. Clinical trials have not shown any advantage from using these antibiotics.

### Treatment of *Stenotrophomonas maltophilia*

*S. maltophilia* is a common cause of infections in healthcare settings, particularly among immunocompromised individuals. β-lactam antibiotics are not effective against *S. maltophilia* infections mainly due to the action of two types of β-lactamase enzymes: a metallo-β-lactamase that hydrolyses all β-lactams except aztreonam, and a serine-β-lactamase. Efflux pumps also play a significant role in *S. maltophilia* resistance to antibiotics, including TMP-SMX. Additionally, *S. maltophilia* is inherently resistant to aminoglycosides due to acetyl transferase enzymes [60,61]. In a retrospective multicenter study conducted using data from the United States Premier Healthcare Database from 2010 to 2015, *S. maltophilia* emerged as the predominant causative agent among carbapenem-resistant gram-negative BSI [62]. Nearly 95% of the isolates showed susceptibility to TMP-SMX, while 84% demonstrated susceptibility to fluoroquinolones. Two treatment approaches are recommended for severe *S. maltophilia* infections. In the first approach, combination therapy of the following antimicrobials should be considered: TMP-SMX, minocycline/tigecycline, cefiderocol or levofloxacin [8▪▪,10]. In the second, a combination of ceftazidime-avibactam and aztreonam is recommended, especially when there is clinical instability or when other medications are not well tolerated or are ineffective [8▪▪].

## CONCLUSION

BSIs due to MDRGNB represent a frequent and severe complication among critically ill patients.



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In recent years, new antimicrobial agents have been developed for treating infections caused by these organisms, alongside the publication of several guidelines providing recommendations for their usage. Rapid diagnostic testing and identification of resistance patterns, in combination with timely antimicrobial stewardship program intervention are crucial for initiating appropriate treatments. Current studies, though limited by their observational design, small number of patients, and evaluation of heterogeneous infections, indicate that the use of new antibiotics is associated with better prognosis in patients with BSI caused by MDRGNB. The issues to be elucidated in the ICU setting include comparing clinical outcomes among the new antibiotics in RCT, the establishment of optimal combination therapies, the identification of the real and potential benefit of prolonged administration of β-lactams, the necessity for therapeutic drug monitoring (TDM) and surveillance of the development of resistance associated with drug use. While guidelines advise TDM for beta-lactam antibiotics in critically ill patients, the precise effect of TDM-guided dosing on clinical outcomes is unclear [63–65].


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## Conflicts of interest

*There are no conflicts of interest.*

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest


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